CLAIMS

1. Library comprising a plurality of tagged non-peptide ligands of formula I

$$(Lig\ J_L)_m\ L\ (J_T\ Tag)_m\ (J_T\ L\ (J_L\ Lig)_m)_p$$

and salts thereof

comprising one or a plurality of same or different ligand moieties Lig each linked to a one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_L

wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is a single bond or is any linking moiety selected from a heteroatom such as N, O, S, P, branched or straight chain saturated or unsaturated, optionally heteroatom containing, $C_{1\text{-}600}$ hydrocarbyl and combinations thereof, which may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

Tag is any known or novel tagging substrate;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L, L J_T and/or – Tag and is at different linking sites in compounds comprising same Lig, J_L, L J_T and/or – Tag.

2. Library as claimed in Claim 1 wherein a GPCR ligand is selected from any compound which is effective as an agonist or antagonist for an adenosine receptor, a beta-adrenoceptor, a muscarinic receptor, a histamine receptor, an opiate receptor, a cannabinoid receptor, a chemokine receptor, an alpha-adrenoceptor, a GABA receptor, a prostanoid receptor, a 5-HT (serotonin) receptor, an excitatory aminoacid

receptor (e.g. glutamate), a dopamine receptor, a protease-activating receptor, a neurokinin receptor, an angiotensin receptor, an oxytocin receptor, a leukotriene receptor, a nucleotide receptor (purines and pyrimidines), a calcium-sensing receptor, a thyroid-stimulating hormone receptor, a neurotensin receptor, a vasopressin receptor, an olfactory receptor, a nucleobase receptor (e.g. adenosine), a lysophosphatidic acid receptor, a sphingolipid receptor, a tyramine receptor (trace amines), a free-fatty acid receptor and a cyclic nucleotide receptor; an inhibitor of intracellular enzymes is an inhibitor of cyclic nucleotide phosphodiesterases; and a substrate or inhibitor of a drug transporter is selected from a substrate or inhibitor of an equilibrium based drug transporters or ATP driven pumps such as a catecholamine transporter, a nucleoside transporter, an ATP-binding cassette transporter, a cyclic nucleotide transporter or derivatives or analogues thereof.

3. Library as claimed in any of Claims 1 and 2 wherein one or more of each -Tag in one or more or each library compound is an entity -Fl and comprises any known or novel fluorophore, whereby the library comprises compounds of which one or more or all of which are of formula I'

$(LigJ_L)_m$ L $(J_T\ Fl)_m$ $(J_T$ L $(J_L Lig)_m)_p$

and an additional Tag may be present which is able to perform a function *in situ*, eg may be any laser activated Tag which is activated to have a local or targetted therapeutic or destructive effect.

4. Library as claimed in any of Claims 1 to 3 wherein each compound of formula I or I' comprises one of a plurality of fluorophores and/or tags providing a library of differently fluorescently tagged ligands comprising one or a number of different fluorophores (preferably of different chemical composition, spectral characteristics etc); and/or providing a library of differently tagged ligands including at least one fluorescently tagged ligand; alternatively each compound of formula I or I' comprises one of a plurality of precursor ligands linked each to one or a plurality of different tags providing a library of same or differently tagged ligands of plural ligand type; alternatively each compound of formula I comprises one of a plurality of linkers linking a precursor ligand and at least one Tag at the same or different linking

site; alternatively each compound of formula I comprises the same linker linking a precursor ligand and at least one Tag at different linking sites providing a library of differently linked tagged ligands of different conformation or anticipated pharmacology and binding.

5. Library as claimed in any of Claims 1 to 4 comprising a plurality of compounds of one or more of formula II to III'':

II $(LigJ_L)_m$ L J_T TagJ_T L $(J_L$ Lig$)_m$ where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1

III $(LigJ_L)_m$ L $(J_T Tag)_m$ where m in each is as hereinbefore defined and is preferably 1 and/or 2, more preferably

Lig J_L – L – J_L Tag and/or

Lig J_L – L – J_T Tag and/or Lig J_L – L – J_T Tag

$\diagdown J_L$ Lig $\diagdown J_T$ Tag

wherein each J_L and J_T comprises J as hereinbefore defined and may be same or different and may derive from functionality originally present in Lig or L and Tag or L or a combination thereof, characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L, L, J_T and/or Tag, and is at different linking sites in the case of any two or more compounds comprising identical Lig, J_L, L, J_T and/or Tag.

6. Library as claimed in any of Claims 1 to 5 including information for each compound of formula I comprised in the Library, relating to the pharmacology for binding to or inhibition of a GPCR receptor or to inhibition of an intracellular enzyme such as cyclic nucleotide phosphodiesterases, or inhibition of or transport by a drug transporter including designation as agonist, antagonist, substrate or inhibitor and measure of affinity or inhibition etc, enabling quantification of results.

7. Library as claimed in any of Claims 1 to 6 wherein Lig is selected from

a) xanthine like structures including XAC, theophylline, caffeine, theobromine, dyphilline, enprofylline and the like; or fused biaryl structures including papaverine, dihydroquinilones such as cilostamide, dipyridamole, vinpocetine and the like; and analogues thereof;

b) adenosine like structures including ADAC, NECA and analogues thereof;

c) ethanolamine like structures including salmeterol, salbutamol, terbutaline, quinprenaline, labetalol, sotalol, bambuterol, fenoterol, reprotolol, tulobuterol, clenbuterol and analogues thereof;

d) oxypropanolamine like structures including CGP12177, propranolol, practolol, acebutalol, betaxolol, ICI 118551, alprenolol, celiprolol (celectol), metoprolol (betaloc), CGP20712A, atenolol, bisoprolol, misaprolol, carvedilol, bucindolol, esmolol, nadolol, nebivolol, oxprenolol, xamoterol, pindolol, timolol and analogues thereof;

e) xanthine like structures including XAC, theophylline, caffeine, theobromine, dyphilline, enprofylline, sildenafil, EHNA (erythro-9-(2-hydroxyl-3-nonyl)adenine), zaprinast and the like; or spiro bicyclic structures including bypyridines such as amrinone, imidazolines such as CI930, dihydropyridazinones such as indolan, rolipram, SB207499, and the like; or fused biaryl structures including papaverine, dihydroquinilones such as cilostamide, dipyridamole, vinpocetine and the like and analogues thereof.

8. Library as claimed in any of Claims 1 to 7 wherein a compound of formula I or I' may optionally comprise functionality J as hereinbefore defined derived from its synthesis by the reaction of one or more reactive group(s) of a linker precursor or its components, providing a linker moiety, with a reactive group of one or more ligand precursors providing a ligand moiety and reaction of one or more other reactive group(s) of the linker precursor with a reactive group of one or more tag precursors such as a fluorescent tag precursor providing a tag moiety.

9. Library as claimed in any of Claims 1 to 8 wherein L is selected from a saturated or unsaturated single or double bond, -O-, -S-, amine, COO-, amide, -NN- hydrazine; and saturated or unsaturated, substituted or unsubstituted $C_{1\text{-}600}$,

preferably C_{1-300}, more preferably C_{1-100} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C_{1-20} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, carbonyl and the like.

10. Library as claimed in any of Claims 1 to 9 wherein J_L and J_T may comprise functionality derived from a reactive group or site for linking to fluorophore and/or to ligand selected from a saturated or unsaturated single or double bond, -O-, -S-, amino, amido, hydrazine, carbonyl, oxo, alkyl, alkenyl, alkynyl, alkoxy, thioxy, and the like.

11. Library as claimed in any of Claims 1 to 10 wherein J_{Lm} L J_{Tm} comprises a mono, di, tri, tetra, penta, or hexa amino, alkylthio, alkoxy, carboxylic acid, and combinations thereof more preferably a mono, di or tri aminoalkylthio, amino alkoxy, alkoxy carboxylic acid, alkoxy amine and the like; preferably J_{Lm} L J_{Tm} is selected from mono, di or tri amino menthane, amino ethane, thio ethane, ethane, amino acyl, from polypeptide, or from mono or polyether derivatives thereof eg diamine or dithio such as mono or polyethylene glycol di or tri amine or thio.

12. Library as claimed in any of Claims 1 to 12 wherein a linker moiety J_{Lm} L J_{Tm} as hereinbefore defined comprises a single or double bond or a single atom or group as hereinbefore defined or comprises a mono-, di-, tri- or tetra, penta or hexafunctional linear or branched or cyclic substituted or unsubstituted hydrocarbyl of formula –L.I-

$$J\,[\,A\,]\,q_L\,R_L\,[\,A'q_{L'}\,J'\,]_{m-1}\,A''q_{L''}\,J''$$

wherein each of J to J'' is a linking site or functionality as hereinbefore defined independently selected from a single bond, methylene, alkyne, alkene, NR, O, NRCO, S, CO, NCO, CHHal, P and the like wherein R is H or C_{1-8} alkyl or

cycloalkyl or forms part of a cyclic ring with N, Hal is any halogen selected from chlorine, iodine, bromine; and is present in any rational location in a group A to A'';

each of A to A '' is a group selected from –O-, -C(=O)-, C_{1-12} alkoxy, alkoyl, cycloalkyl, heterocyclic, alkyl, alkenyl, aryl, arylamide, arylamine, amino, thioalkyl, heteroaryl as hereinbefore defined and combinations thereof and the like, optionally substituted by groups selected independently from C_{1-3} alkyl, C_{1-5} alkoxy and the like;

each of q_L to q_L'' are independently-selected from 0 or 1 or indicates an oligomeric repeat and is from 2 to 30, or indicates a polymeric repeat unit and is from 31 up to 300.

R_L is a C, N or S atom or is a $CR_{L'}$, $NR_{L'}$, alkyl, cycloalkyl, heterocyclic, aryl heteroaryl, amine or thio moiety and provides for branching when p is 1 or 2; wherein $R_{L'}$ is H or C_{1-3} alkyl; and

p is as hereinbefore defined and is 0, 1 or 2.

13. Library as claimed in any of Claim 12 wherein each J, J' and J'' independently is a single or double bond, NR_L, -O or –S or –C(O) or -NRC(O) or -C(O)NR, as hereinbefore defined

A is alkoxy preferably CH_2CH_2O (PEG) and oligomers thereof or is aralkylamine aralkylamide, aralkyloxy, or is alkyl, preferably $(CH_2)_{1-12}$

R_L is a C_{1-5} alkyl chain comprising or containing a single or double branching C atom when p is 1 or 2;

p is 0, 1 or 2;

A' and A'' are each selected from C_{1-8} alkyl, amine, phenylamine, phenylamide; and

q_L is 0, 1, 2 to 30 or 31 to 300, and $q_{L'}$ and $q_{L''}$ are 0 or 1

14. Library as claimed in any of Claims 12 to 13 wherein J_{Lm} L J_{Tm} is a single bond or is of formula

J Aq_L R_L J''

wherein each of J and J'' is amine or –O- , A is CH_2CH_2O, q_L is 1-30 or 31 to 300 and R_L is CH_2CH_2

or of formula

J Aq_L R_L(A'J') J''

wherein each of J, J' and J'' independently is amine, –O or a single bond, q_L is 1, 2 or 3 -30 or 31 to 300 and A is CH_2CH_2O or $HNCH_2CO$ or q_L is 1 and A is C(O) or $(CH_2)_{1-8}$ or q_L is 0, R_L is CH or CH_2CH, $q_{L'}$ is 0 or q_L' is 1 and A' is CH_2 and $q_{L''}$ is 0 preferably

$O(CH_2CH_2O)q_LCH_2CH_2NH$, $O(CH_2CH_2O)q_LCH_2CH(CH_2NH)NH$,

$OCH(CH_2NH)NH$, -$CH(CH_2NH)NH$, -C(O) NH-, -$(CH_2)_{1-8}$-, (-$HNCH_2CO$-)$_{1-3}$ (= -gly_{1-3}-) - or the like.

15. Library as claimed in any of Claims 1 to 14 wherein each compound of formula I or I' as hereinbefore defined comprises a moiety Lig and L as hereinbelow defined:

Wherein:

Lig.a_m is suitably of the formula, in either of the following forms given, including any of its possible linking configurations or sites:

Lig.$a^1{}_m$

Wherein any or each of Ra^1 to Ra^4, X^1 and X^2 may comprise a linking site or functionality J as hereinbefore defined

X^1 and X^2 are each independently selected from H, O, OR.a, NR.a, NHR.a;

X^1 and X^2 are each preferably O;

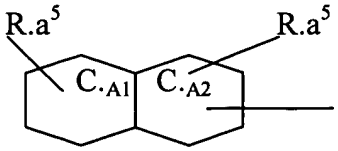
each of R.a, $R.a^1$, $R.a^2$ and $R.a^3$ independently is selected from H or C_{1-4} linear or branched alkyl, preferably H, methyl, ethyl, n-propyl,

isopropyl, n-butyl, t-butyl or isobutyl optionally mono or multi hydroxy or halo substituted, such as CH_2OH, CH_2F or $CH_2CHOHCH_2OH$;

R.a^4 is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted $C_{1\text{-}20}$ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any $C_{1\text{-}12}$ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

preferably R.a^4 is selected from optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, more preferably optionally substituted alkoxy, cycloalkyl, amine, amide, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl etc, for example substituents include, or R.a^4 comprises, cyclohexyl, cyclopentyl, ethoxy, $(CH_2)_2PhPh$, CH_2Ph, $CONH(CH_2)nCONH$, $CH_2CONH(CH_2)_2NH$, $CH_2PhNHCOCH_2$, $CH_2CH_2OCOCH_2$, succinimidyl ester, $NHCOCH_2$, $CH_2(CH_3)NCOCH_2$, $H_2N(CH_2)_2NHCOCH_2$, $H_2N(CH_2)_8NHCOCH_2$, $H_2NNHCOCH_2$, $CH_2CONH(CH_2)_2NHCOCH_2$, $HOPhCH_2N(CH_2CH_3.HOAc)(CH_2)_2NHCOCH_2$, heterocyclic-$(CH_2)_4CONH(CH_2)_2NHCOCH_2$, heterocyclic-$NHCON$(heterocyclic)$COCH_2$ and the like;

or Lig.a is of the formula Lig.a^2-

Lig.a^2 

wherein any or each of Ra^5 to Ra^6, or a cyclic C or heteroatom may comprise a linking site or functionality J as hereinbefore defined each of $C._{A1}$ and $C._{A2}$ is independently selected from C_{5-6} aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring –C=C- group;

Each of up to seven $R.a^5$ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH_3, $CH_2Ph(OCH_3)_2$, $O(CH_2)_3CON(CH_3)$c.hex, $N(CH_2CH_2OH)_2$, c.hex, $COOCH_2CH_3$, CH_2CH_3;

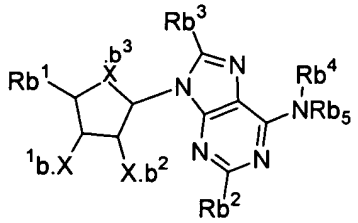
or any two or more of $R.a^5$ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic $Lig.a^2$structure;

and $R.a^6$ is a moiety as defined for $R.a^5$ above;

and L.ais as hereinbefore defined for L or J_L L J_T and is suitably of formula L.I or subformulae as hereinbefore defined, more preferably is selected from a single bond, amino acid or amide such as a peptide or polypeptide for example gly or gly_3, alkyl of formula $-(CH_2)_n$ where n is 3 to 8, preferably 3, 4 or 6, optionally including one or more heteroatoms or unsaturated groups, such as –O- or –S- or –CH=CH- and the like:

Lig.b is suitably of the formula Lig.b including any of its possible linking configurations or sites:

Lig.b



wherein any or each of Rb^1 to Rb^5 or Xb^1 to Xb^3 may comprise a linking site or functionality J as hereinbefore defined

ring substituents $X.b^1$ and $X.b^2$ are independently selected from hydrocarbon such as alkyl or SR_X, $NR_{X.2}$ and OR_X wherein (each) R_X is selected from H, C_{1-5}alkyl, alkenyl;

ring heteroatom $X.b^3$ is selected from –S-, -O- and $–CH_2$-;

Rb^1 is selected from saturated or unsaturated, substituted or unsubstituted C_{1-4} aliphatic, or C_{1-3} alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; preferably $R.b^1$ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C_{1-3} alkyl, cycloalkyl or amide, more preferably cyclopropyl, or $CONHC_{1-3}$alkyl such as CONHEt or CH_2OH

and each of $R.b^2$ and $R.b^3$ is selected from H, halo, hydroxy, thiol, amine, COOH, CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, preferably from H, halo or hydroxy, preferably H or Cl;

Rb^4 is H;

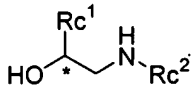
Rb^5 is H or alkyl

L.b may comprise a linking site or functionality J as hereinbefore defined; and

is as hereinbefore defined for L or its subformulae, more preferably is saturated and unsaturated substituted or unsubstituted C_{1-12} aliphatic or C_{1-24} aromatic as defined for L preferably including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, more preferably is of formula L.I or its subformulae as hereinbefore defined, most preferably is (CH_2)m wherein m is 2 to 12, preferably 3, 4, 6 or 8, or is (Ph-$CH_2CONH)_2$ $(CH_2)_2$;

Lig.c is suitably a non-peptide of the formula Lig.c including any of its possible linking configurations or sites:

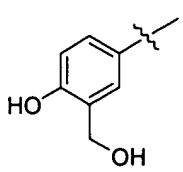
Lig.c $HOC^*(R.c^1)CH_2NH\text{-}R.c^2$



Where any or each of Rc^1 to Rc^2 or OH, or a chain C or N may comprise a linking site or functionality J as hereinbefore defined

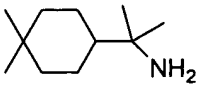
* indicates an optically active centre and

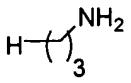
Wherein $R.c^1$ is C_{6-14} aryl optionally including one or more heteroatoms selected from H, O, optionally substituted by OH, Hal eg Cl, NH_2, NHC_{1-3}alkyl, sulphonamide, oxoamine (-$CONH_2$) and the like, more preferably mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH_2, more preferably m-CH_2OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m-,m-diCl, p-NH_2 phenol, p-OH, m-$CONH_2$ phenol or 5-OH, 8-quinoline and the like, such as



$R.c^2$ is selected from saturated or unsaturated, substituted or unsubstituted C_{1-20}, preferably C_{1-12}, branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like and combinations thereof;

Preferably $R.c^2$ is selected from C_{1-6} branched or straight chain aliphatic, C_{6-10} araliphatic optionally substituted by OH and optionally including heteroatoms selected from N,O, preferably including an ether O, such as selected from $-(CH_2)_6OCH((CH_2)_3Ph)$, $CHCH_3(CH_2)_2Ph$, $CHCH_3CH_2PhOH$, $C(CH_3)_2CH_2$ or from the structures:

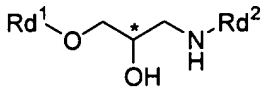




L.c may be present as $R.c^2$ or may comprise a linking site or functionality J as hereinbefore defined, and is as hereinbefore defined for L and is suitably of formula L.I or its subformulae as hereinbefore defined, more preferably is selected from C_{1-12} alkyl, amide etc;

Lig.d is suitably a non-peptide of the formula Lig.d including any of its possible linking configurations or sites:

Lig.d $R.d^1\ OCH_2C^*HOHCH_2NH\text{-}R.d^2$



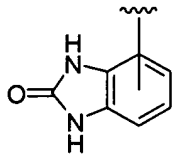
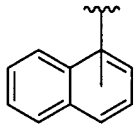
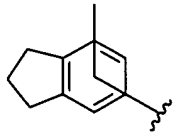
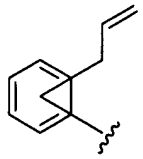
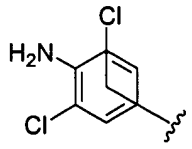
where any or each of Rd^1 to Rd^2 or OH, a chain C or N may comprise a linking site or functionality J as hereinbefore defined

* indicates an optically active centre

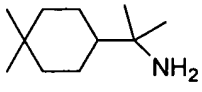
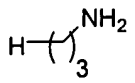
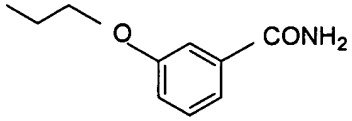
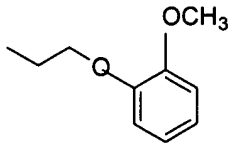
Wherein $R.d^1$ is saturated or unsaturated, substituted or unsubstituted $C_{1\text{-}20}$ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any $C_{1\text{-}12}$ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

Preferably $R.d^1$ is substituted or unsubstituted $C_{1\text{-}24}$ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include $C_{1\text{-}6}$ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH subtitited, or halo such as chloro or OH, preferably $R.d^1$ is unsubstituted or substituted alkyl, alkenyl, halo, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, illustrated as follows, most preferably mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl such as phenyl, carbazole or structures shown below or spiro ring systems, most preferably mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF_3 substituted phenyl or

unsubstituted or monosubstituted naphthalene or 5,6 ring systems most preferably of the structures:

R.d^2 is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C_{1-12} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, more preferably amine, C_{1-6} branched or straight chain alkyl optionally including ether O, and

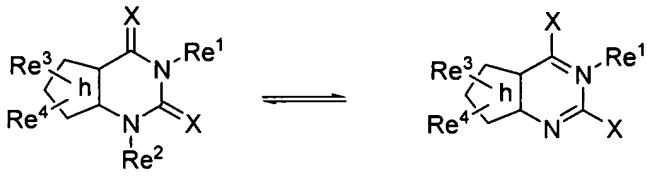
optionally substituted by C_{6-10} aryl, for example i.pr, i.bu, or of the formula:

L.d may be present as R.c^2 or may comprise a linking site or functionality J as hereinbefore defined and is as hereinbefore defined for L and its subformulae and is suitably of formula L.I and its subformulae as

hereinbefore defined, more preferably is a single bond or is as hereinbefore defined for L.a;

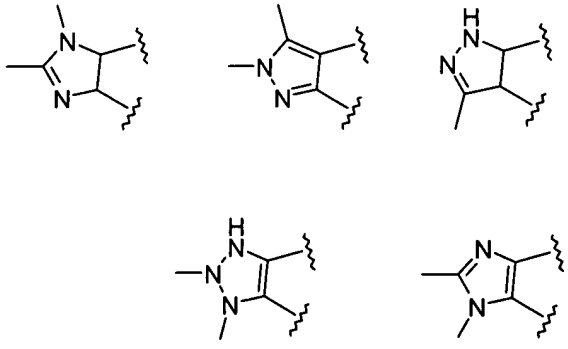
Lig.e comprises a cell permeant moiety or is associated with a cell permeant L or Fl moiety and is suitably of the formula , in either of the following forms given including any of its possible linking configurations or sites:

Lig.e[1]



wherein any or each of Re^1 to Re^4, X and a ring C or N may comprise a linking site or functionality J as hereinbefore defined

h is selected from



each optionally substituted by $R.e^3$ – $R.e^4$ wherein $R.e^1$ – $R.e^4$ are as $R.a^1$ – $R.a^4$ defined above or in which $R.e^3$ is C_{5-9}linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy, sulfonyl and the like

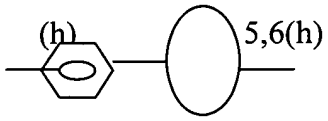
eg ortho-OEt, meta- SO_2N NCH_3

each X is independently selected from H, O, -OR.e^2, N, HN, NR.e^5, HR.e^6 , and aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted such as Ph-ortho-$OCH_2CH_2CH_3$;

and where R.e^5 is as defined above for R.e^1 above or forms a fused cyclic ring together with the adjacent ring N atom; preferably 1 or 2 fused 5 membered cyclic rings;

and R.e^6 is as defined above for R.e^1 above or is selected from optionally substituted phenyl wherein optional substituents include ether such as o-ethoxy or o-propoxy, alkyl, OH and the like, sulphonyl, carbonyl and the like substituted by heterocyclic, or cyclic C_{5-8} alkyl such as methyl, piperazinyl, sulphonyl and the like;

or Lig.e is of the formula Lig.e^2

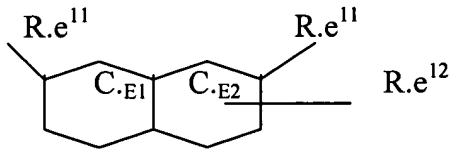
Lig.e^2 

Wherein any or each free ring atom or their substituents may comprise a linking site or functionality J as hereinbefore defined

each spiro ring optionally comprises zero or one or more heteroatoms h which are preferably N, more preferably (h)  comprises zero or 1 N heteroatom and  5,6(h) comprises zero, 1 or 2 N heteroatoms and is unsaturated or comprises one or two –C=C- or -C=N- groups;

and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C_{1-6} alkyl or linear or cyclic alkoxy such as methoxy, ethoxy or cyclopentyloxy optionally substituted by one or more oxo, CO, COOH, CN, or C_{1-6} alicyclic or amine groups, amine or one or more spiro or fused heterocycles;

or Lig.e is of the formula Lig.e^3

Lig.e^3 

Wherein any or each of Re^{11} to Re^{12}, or a ring C or heteroatom or ring substituent may comprise a linking site or functionality J as hereinbefore defined

each of $C._{E1}$ and $C._{E2}$ is independently selected from C_{5-6} aryl, heteroaryl, cyloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring –C=C- group;

Each of up to seven R.e^{11} is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH_3, $CH_2Ph(OCH_3)_2$, $O(CH_2)_3CON(CH_3)$c.hex, $N(CH_2CH_2OH)_2$, c.hex, $COOCH_2CH_3$, CH_2CH_3;

or any two or more of R.e^{11} form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e^3 structure;

and R.e^{12} is a moiety as defined for R.e^{11} above;

Preferably Lig.e is of the formula Lig.e^1 as hereinbefore defined in particular where R.e^2 and R.e^3 are respectively propyl and butyl;

L.e may comprise a linking site or functionality J as hereinbefore defined and is suitably as hereinbefore defined for L.a.

16. Library as hereinbefore defined in any of Claims 1 to 15 wherein Fl is selected from dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules such as Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the comercially available Bodipy™ dyes, erythosin, eosin, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™ including the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups and other red, blue or green absorbing fluorescent dyes in particular red absorbing dyes as reviewed in Buschmann V et al, Bioconjugate Chemistry (2002), ASAP article.

17. Library as claimed in Claim 16 wherein J_T – t - Fl comprising a BODIPY ™ structure is characterised by a dipyrromethene boron difluoride core, optionally modified by one or two fused rings, optionally substituted by one or several substituents such as alkyl, alkoxy, aryl, heterocyclic and the like, wherein one substituent –t- is adapted for linking as hereinbefore defined to a ligand precursor as hereinbefore defined, the substituent –t- optionally comprising a proximal unsaturated or aryl moiety, comprising a medial short, medium or long chain alkynyl or cycloalkyl moiety and comprising a moiety derived from linking via a reactive group as hereinbefore defined such as carboxyl, sulphonate or as a heteroatom such

as O or S or methylene derived from linking at an alkylhalide such as methylbromide, haloacetamide, sulphonate ester or the like electrophilic group.

18. Process for the preparation of a library as hereinbefore defined comprising the reaction of one or each of a plurality of ligand precursors and tag precursors comprising linker moieties or ligand, tag and linker precursors wherein linking may be at same or different reactive sites in different compounds as hereinbefore defined.

19. Process as claimed in Claims 18 which is a combinatorial process; preferably comprises the reaction of one or more ligand precursors of formula IV and/or IV'

IV $(LigJ_L)_m - L - Y_{Ln}$

IV' $Lig\ Y_{Lign}$

comprising one or more or different reactive groups Y_L or Y_{Lig} forming a linking functionality J, J_L or J_T as hereinbefore defined

with one or more of a plurality of analytical tagging substrates of formula V and/or V'

V $Y_{Tm}\ Tag$

V' $Y_{Tm}\ L\ (J_T Tag)_m$

comprising one or more or different reactive groups Y_T forming a linking functionality J or J_T as hereinbefore defined

and optionally one or more linking species VI or VI' or VI''

VI $Y_{Lm}\ L\ Y_{Lm}$

wherein Lig, J, L, J_T and Tag and each m is independently as hereinbefore defined

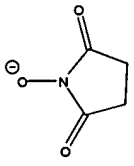
wherein the or each compound of formula IV or IV' is capable of reaction with the or each compound of formula V or V', optionally via the or each species VI or VI' or VI'' to form a plurality of compounds of formula I as hereinbefore defined.

20. Process as claimed in Claim 18 or 19 wherein reactive groups Y_{Lig}, Y_L, Y_T have suitable reactive group functionalities for linking, as hereinbefore defined, for example by substitution or by addition or addition – elimination reaction.

21. Process as claimed in Claim 20 wherein substitution reaction is selected from reaction of electrophilic and nucleophilic reactive sites as hereinbefore defined:

Electrophilic Y	Nucleophilic Y	Resulting covalent Linkage, J	leaving groups
Carboxylic acid	alcohol	ester	-OH, -H
Carboxylic acid	amine	carboxamide	-OH, -H
Carboxylic acid	hydrazine	hydrazide	-OH, -H
Alkyl halide	alcohol	ether	-Hal, -H
Alkyl halide	thiol	thioether	-Hal, -H
Alkyl halide	amine	alkylamine	-Hal, -H
Alkyl halide	COOH	ester	-Hal, -H
Haloacetamides	thiols	thioethers	-Hal, -H
Sulphonate esters	amines	alkyl amines	RSO_3-, -H
Sulphonate esters	alcohols	ethers	RSO_3-, -H
Sulphonate esters	thiols	thioethers	RSO_3-, -H
Sulphonyl halides	amines	sulphonamides-Hal,	-H
Sulphonyl halides	alcohols	sulphonate esters	-Hal, -H
Succinimide ester	alcohols	esters	-OSu*, -H
Succinimide ester	alkoxides	esters	-OSu*, H or M^+
Succinimide ester	thiols	thioesters	-OSu*, -H
Succinimide ester	amine	carboxamide	-OSu*, -H
Succinimide ester	hydrazine	hydrazide	-OSu*, -H

wherein * is



and addition reaction is suitably selected from cycloaddition or addition-elimination reaction of electrophilic and nucleophilic reactive sites in IV and V as hereinbefore defined:

Electrophile	Nucleophile Covalent	Leaving

Y Group	Y	Linkage, J	
azide	alkyne	triazole*	none
2-acyl cyclic mono-	dinucleophile	6,7-dihydro-1H-indazol-4(5H)-one	H_2O
/di-ketone	eg hydrazine	4,5,6,7-tetrahydro-1H-indazole	H_2O
(5 or 6 mem ring)		1,4,5,6-tetrahydrocyclopenta[c]pyrazole	H_2O
		5,6-dihydrocyclopenta[c]pyrazol-4(1H)-one	H_2O

wherein * is [3+2] dipolar cycloaddition.

22. Process for the preparation of a compound of formula I as hereinbefore defined in any of Claims 1 to 17 comprising the reaction of a compound of formula IV or IV' and a compound of formula V or V' and optionally additionally VI, as hereinbefore defined.

23. Process for the preparation of a compound of formula IV as hereinbefore defined in any of Claims 18 to 21 comprising: obtaining where commercially available or preparing the ligand precursor Lig, by routes as known in the art, and reacting with linker precursor VI'', if required, or components thereof, and/or generating one or more reactive sites Y or Y_{Lig} or Y_L.

24. Method for selecting a compound of formula I from a library as hereinbefore defined comprising the rational design of a library of compounds of formula I as hereinbefore defined using the process as hereinbefore defined, determining pharmacology for a plurality of or all compounds in the library and selecting a compound exhibiting desired pharmacology.

25. Method as claimed in Claim 24 which comprises preparing a preliminary library of compounds, conducting screens to assess binding, inhibition and the like, selecting compound identified in the screen as having beneficial properties, and modifying or functionalising by nature of moieties or linking location of linking on the basis of the indications from the screen to prepare an optimised library. In a

particular advantage of the invention the molecular pharmacology and photochemistry from the screen feedback into the design of the library.

26. Compound of formula I or I' as hereinbefore defined in any of Claims 1 to 17 wherein the compound is associated with information relating to its pharmacological properties in the form of Spectral Properties given as Excitation Max and Emission Max, Fluorescence Lifetime and Emission quantum yield and Pharmacology defined in terms of cells expressing a GPCR receptor as hereinbefore defined or expressing an intracellular enzyme such as a cyclic nucleotide phosphodiesterase, or a drug transporter as hereinbefore defined and given as the Inhibition or Antagonism of receptor binding or of receptor functionality together with a value for the Inhibition (pK_B) or Antagonism (pK_I) binding constants, and optionally together with fluorescent images of the pharmacological binding in single living cells illustrating the defined inhibition or antagonism, preferably the pharmacological properties are given as EC_{50} values for agonist stimulated – or pK_i values for antagonism of agonist stimulated second messenger generation, or substrate K_m values or antagonist K_i values for stimulation or inhibition of intracellular enzymes or drug transporters..

27. Compound of the formula I or I' as hereinbefore defined in any of Claims 1 to 17 selected from formulae Lig.a_m L.a-Fl.a_n to Lig.e_m L.eFl.e_n as hereinbefore defined

with the proviso that:

a) when Lig is XAC ie in Lig.a when each of R.a^1 and R.a^2 is propyl, R.a^3 is H and R.a^4 is –Ph-$OCH_2CONH(CH_2)_2NH$-, and L is a single bond or L is gly and n=3 or L is NCS, Fl is not fluorescein; or

when Lig is XAC and L is a single bond or NCS, Fl is not fluorescein or NBD;

b) when Lig is adenosine Fl is not Fmoc (CA 134:204756); or

when Lig is ADAC , ie R.b^1 is CH_2OH, R.b^2 and R.b^3 are H and L is –(Ph-$CH_2CONH)_2(CH_2)_2$- or L is a single bond, Fl is not fluorescein, NBD or Rhodamine; or

when Lig is NECA (incorporating the moiety $-(CH_2)m$) ie $R.b^2$ and $R.b^3$ are H and L is a single bond, or is $-(CH_2)m$ when m is 2,4,6,8 or 10 then Fl is not NBD, or when m is 3,4,6,8,10 or 12 then Fl is not dansyl; or

when Lig is N^6-[2-(4-aminophenyl)ethyl]adenosine and L is $(CH_2)_2PhNH$, Fl is not FITC (CA 131:56155 (8))

d) when Lig is CGP12177 and L ($R.d^2$) is mono amine menthane, Fl is not BODIPY® TMR; or

when Lig is CGP12177 and L is 1,1,4,4-tetramethyl butylamine, i.e $C(CH_3)_2(CH_2)_2C(CH_3)_2NH$- Fl is not BODIPY® FL, or when L is $C(CH_3)_2(CH_2)_2C(CH_3)_2NHCSNH$- then Fl is not FITC, eosin or erythosin; or when L is monoamine menthane, Fl is not FITC (CA 131:56155 (4)); or

when Lig is CGP12177 and L is a single bond, Fl is not NBD; or

when Lig is alprenolol i.e o-prop-2-enyl phenyl and L is $-C(CH_3)_2$- or a single bond, Fl is not NBD;

optionally additionally

a) when Lig is XAC ie in Lig.a when each of $R.a^1$ and $R.a^2$ is propyl, $R.a^3$ is H and $R.a^4$ is $-Ph-OCH_2CONH(CH_2)_2NH$-, and L is a single bond Fl is not BODIPY ™ 630/650; or

b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650.

28. Compound of formula IV or IV' or library thereof as hereinbefore defined in any of Claims 18 to 21 useful for linking to any suitable tag of formula V or V' as hereinbefore defined in any of Claims 18 to 21 ,

with the proviso that

when Lig is Lig.a and is 1,3-dialkyl xanthine as hereinbefore defined wherein X^1 and X^2 are =O, $R.a^3$ is H, $R.a^1$ and $R.a^2$ are both CH_3 or both n-C_3H_7, then $R.a^4$ is not 4-hydroxyphenol or $PhOCH_2CO_2H$; or

when $R.a^1$ and $R.a^2$ are both n-C_3H_7, then $R.a^4$ is not $PhOCH_2OCNHPhOH$; $PhOCH_2OCONsuccin$, $PhOCH_2CONH_2$, $PhOCH_2CONH(CH_2)_2NH_2$, $PhOCH_2CONH(CH_2)_8NH_2$, $PhOCH_2COHNNH_2$, or $PhOCH_2CONH(CH_2)_2N(CH_2CH_3.HOAc)CH_2PhOH$; or

when Lig is CGP12177 then L is not $-C(CH_3)_2(CH_2)_2C(CH_3)_2NH_2$ (CA 121:103486; or

when Lig is aden, L is not $-(CH_2)_2S(CH_2)_2NH_2$ (CA 125:218348; or L is not $(CH_2)_6NH_2$ or $CH_2CONH(CH_2)_6NH_2$ (CA 134:2043); or L is not $(CH_2)_2NH_2$ or $(CH_2)_2O(CH_2)_2O(CH_2)_2NH_2$ (CA 135:25706); or L is not $(CH_2)nNH_2$ where n is 2 – 12 (CA 108:715);

or when Lig is alprenolol L is not $(CH_2)_8NH_2$ or when Lig is propranolol L is not $(CH_2)_4NH_2$ (CA 124:8848)

or when Lig is alprenolol L is not $CH_2C(CH_3)_2NH_2$ (CA 108:215827)

or when Lig is ICI 118551 L is not $(CH_2)_2NH_2$ or when Lig is propranolol L is not $(CH_2)_2NH_2$ (CA 98:4564)

29. Fluorophore linker of formula V or V' as hereinbefore defined in any of Claims 18 to 21.

30. Kit comprising ligand precursors, linker precursors and tag precursors of formulae IV, IV', V, V' and/or VI as hereinbefore defined in any of Claims 18 to 21, 27 or 28 for preparing a library of compounds of formula I as hereinbefore defined in any of Claims 1 to 17.

31. Use of a fluorescent ligand of formula I or I' or library thereof as hereinbefore defined in any of Claims 1 to 17 for visualising receptors or receptor binding, assessing pharmacological properties of the fluorescent ligand, in high throughput screening of novel chemical entities that bind to the target receptor, in inhibiting an intracellular enzyme or inhibiting a drug transporter or a substrate of a drug transporter, in studying drug transport or drugs suitable for transport, in distinguishing healthy or diseased tissue and the like.

32. Method for receptor binding or inhibition, intracellular enzyme inhibition or drug transport or inhibition and visualisation comprising contacting a compound of formula I or I' as hereinbefore defined in any of Claims 1 to 17 or 27 with a sample

in manner to facilitate binding or inhibition thereof or transport thereby, and detecting changes in fluorescence or location thereof.

33. Method as claimed in Claim 32 wherein a sample comprises cell material selected from cells, cell extracts, cell homogenates, purified or reconstituted proteins, recombinant proteins or synthesised proteins and the like and includes a target for the compound of formula I.

34. Method as claimed in any of Claims 32 and 33 wherein a sample comprises live cell material, more preferably including individual cells or sub cell compartments, most preferably comprises GPCRs, intracellular enzymes or drug transporters in living cells, membrane containing these proteins, solubilised receptors, enzymes or drug transporters or GPCR arrays.

35. Method as claimed in any of Claims 32 to 34 wherein cell material is tagged prior to contact with the fluorescent ligand, for example by tagging with GFP, for example GFP tagged GPCR's, GFP tagged intracellular enzymes and GFP tagged drug transporters, or a native receptor, intracellular enzyme or a drug transporter to which a fluorescent antibody has been targetted, to allow visualising of the cell receptors, enzymes or transporters, and overlay with the fluorescent ligands.

36. Use of a fluorescent target for the method as claimed in any of Claims 32 to 35 for example, a Green Fluorescent Protein-tagged receptor, intracellular enzyme or drug transporter.

37. Use as claimed in Claim 36 wherein cross-correlation fluorescence correlation spectroscopy or fluorescence intensity measurements allow the quantitative analysis of ligand-receptor, ligand-enzyme, ligand-drug transporter or drug transport interactions in a single measurement.

38. A cell surface GPCR modified on its N-terminus or a naturally occurring domain to express a short epitope tag for a commercially available fluorescent

antibody for use in living cells to provide two-colour analysis of fluorescent ligand-receptor interactions.

39. CHO cells expressing a cell surface GPCR modified as claimed in Claim 38 for use with a fluorescent antibody to the tag sequence for use in living cells to provide two-colour analysis of fluorescent ligand-receptor interactions.

40. A kit comprising a compound of formula I or I' as hereinbefore defined in any of Claims 1 to 17 or 27 and a target therefor provided as a cell line, expressing a GPCR, intracellular enzyme or drug transporter, membrane containing these proteins derived from such a cell line, solubilised receptor, enzyme or drug transporter or GPCR array from that cell line.

41. Kit as claimed in Claim 40 wherein the cell derived material is provided in one of three forms: (1) from cells expressing a green fluorescent protein tagged receptor, intracellular enzyme or drug transporter; (2) from cells expressing an epitope tag for a commercially available fluorescent antibody or (3) a wild-type protein for which a specific fluorescent antibody is also provided.

42. Kit as claimed in Claim 39 or 40 comprising a compound of formula I or I' as hereinbefore defined in any of Claims 1 to 17 or 27 and a fluorescent antibody to a native protein which can be used in native (non-recombinant) cells.

43. Library, compound, precursor, process, method, target material or kit as hereinbefore described or illustrated in the description, examples and/or figures.